UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/704,445

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/704,445	[illegible]	[illegible]	B 103962001301

EXAMINER

18N2/0930

ANTOINETTE F KONSKI
MORRISON & FOERSTER
755 PAGE MILL ROAD
PALO ALTO CA 94304-1018

ART UNIT	PAPER NUMBER
1804	20

DATE MAILED: 09/30/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/26/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three (3) month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). #18
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948

This application should be reviewed for errors.

Claims 1-31 are examined in this Office Action.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure. Applicants have disclosed transplantation of human thy/liv explants into immunocompromised mice and subsequent injection of liposome-encapsulated dichloromethylene diphosphonate (DMDP) to decrease the number of endogenous macrophages in the mouse. Applicants then monitored the depletion of macrophages by acid phosphatase staining and monitored the presence of human cells by the intensity of the CD45+ cell surface marker, using an antibody to human leukocytes.

Regarding claims 1-12 and 14-31, the claims must be limited to a non-human animal since the specification fails to provide the guidance necessary to show the invention would work as claimed in humans. Applicants have not provided guidance regarding the route of administration, amount, time course, number of treatments which would enable one of ordinary skill to practice the invention as claimed without undue experimentation. In addition, the relationship between HIV infection and macrophage depletion is not elucidated in the specification and HIV infection in conjunction with DMDP treatment would appear to result in depletion, not prevention of depletion, of non-autologous hematopoietic cells.

Regarding claims 10 and 11, the claims must be limited to DMDP treatment since both radiation therapy and chemotherapy would possibly ablate the entire endogenous immune system, thereby rendering the DMDP treatment moot. Further, the specification fails to provide guidance to one of ordinary skill regarding the types and protocols of chemotherapy or radiation therapy which would transiently immunocompromise the host immune system and yet allow the DMDP treatment to kill macrophages. The specification fails to provide guidance as to the interaction of radiation/chemotherapy with DMDP treatment and fails to present evidence that the combination of systems would result in depletion of macrophages.

Regarding claim 31, the specification fails to disclose methods for ablating in whole or in part the endogenous stem cell population of the host animal. The specification fails to disclose methods for ablating the endogenous stem cell population and there are no known methods in the art which would preferentially ablate only the stem cells and not any of the other hematopoietic cells. Further, the specification fails to disclose which part of the endogenous stem cell population may be ablated and how the ablation is to occur. The known methods of radiation and chemotherapy ablate dividing cells and therefore ablate all mature, immature and progenitor cells and would therefore ablate the macrophages as well. There is no teaching in the specification regarding methods of ablating non-dividing cells such as stem cells. In view of the lack of guidance in the specification regarding the method for ablating only stem cells and in view of the lack of knowledge in the art of ablation regimens targeting only stem cells, it would require undue experimentation by one of ordinary skill to develop the methodology necessary to practice the invention as claimed.

Claims 1-12 and 14-31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 31 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "in whole or in part" is vague and unclear since the metes and bounds of "in part" are not clear.

Claims 1-23 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "substantially" is vague and unclear since the metes and bounds are undefined.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant

is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-17 and 19-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Aldrovandi et al. taken with Pinto et al. Aldrovandi discloses the SCID-hu mouse as a model for HIV infection. Aldrovandi discloses that mice homozygous for the SCID genetic defect were transplanted with human fetal hematopoietic tissues and that human fetal liver and human fetal thymus transplants were infected with HIV-1. Aldrovandi discloses that the human thy/liv implants stained for both the CD4 and CD8 markers whereas the infected thy/liv implants showed a depletion of CD4+ cells. Aldrovandi further discloses that their data suggest that HIV-1 infection of the SCID-hu mouse reproduce key aspects of HIV-1 pathology in man and may be an important small animal model to study HIV-1 induced pathogenesis in vivo. Aldrovandi discloses that "The SCID-hu mouse system does not merely reproduce in vitro phenomenon, but allows infection of primary cells to be studied in a more appropriate environment. This model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system". Aldrovandi differs from the claims in that the reference fails to disclose decreasing the number of endogenous macrophages to a level to prevent depletion of the non-autologous hematopoietic cells. However, the secondary reference, Pinto et al., cures the deficiency. Pinto discloses that administration of dichloromethylene diphosphonate (DMDP) encapsulated in liposomes and administered intravenously will selectively deplete tissue splenic and liver macrophages. Pinto further discloses that the endogenous lymphocytes undergo leukocytosis, which is rapid proliferation of lymphocytes. Thus, it would have been obvious to

one of ordinary skill to modify the method of Aldrovandi by treating the SCID-hu mice with DMDP in order to kill the endogenous macrophages since Pinto also teaches that the DMDP liposome depletion system had been shown to diminish the humoral immune response to certain antigens in the spleen, and more importantly, had been shown to stimulate lymphocyte division. By diminishing the endogenous immune response by depleting the macrophages, one of ordinary skill would have had a reasonable expectation that the autologous (human) cells of the thy/liv transplant would survive longer and would also expect a stimulation of the autologous (human) lymphocytes in view of the leukocytosis effect seen by Pinto on the endogenous lymphocytes.

Regarding claims 2 and 15, the administration of autologous cells by administration is not seen to be different than administration by transplantation since the net effect, the stimulation of leukocytosis by DMDP and simultaneous depletion of macrophages by DMDP would still result.

Regarding claim 6, the use of mice having naturally occurring low levels of macrophages would be obvious to one of ordinary skill since the purpose of the use of DMDP is to reduce the levels of macrophages.

Regarding claims 9 and 17, Aldrovandi discloses that the SCID-hu mouse infected with HIV-1 reproduces key aspects of HIV-1 pathology in man and may be an important small animal model to study HIV-1 induced pathogenesis in vivo and that the model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system. Thus, it would have been obvious to one of ordinary skill to apply the method of Aldrovandi modified by Pinto to humans having HIV infection since Pinto teaches that macrophage depletion interferes with the immune response and also stimulates lymphocyte production. Transplanted autologous T cells, or bone

marrow or PBL would not be rejected in view of the teachings of Pinto the DMDP interferes with the immune response.

Regarding claims 10 and 11, ablation of the immune system to deplete the host of immune responding cells would be obvious in view of the teachings of Aldrovandi that the host must be immunocompromised (SCID) in order to allow transplantation of autologous tissue.

Regarding claims 19-23, the combination of references renders obvious the non-human mammal since Aldrovandi discloses SCID-hu mice containing human hematopoietic cells and Pinto discloses use of DMDP to inactivate macrophages.

Aldrovandi provides the motivation to combine the references. Aldrovandi discloses that "The SCID-hu mouse system does not merely reproduce in vitro phenomenon, but allows infection of primary cells to be studied in a more appropriate environment. This model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system". It would have been obvious in view of those teachings to treat hosts having HIV-1 infection with DMDP since DMDP is known to inactivate macrophages, a known source of HIV infection, in order to abolish a viral reservoir.

Accordingly, the modification of the method of Aldrovandi by additionally using DMDP to inactivate macrophages as suggested by Pinto in order to obtain a method of preventing depletion of non-autologous hematopoietic cells was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 18 is rejected under 35 U.S.C. § 103 as being unpatentable over Aldrovandi and Pinto as applied to claims 1-18 above, and further in view of Bernstein et al. Claims 1-18 were rejected for reasons as stated above. Bernstein discloses (page 544, column 1 first paragraph) that macrophage growth factors such as GM-CSF, M-CSF and IL-3 may enhance HIV replication in mononuclear phagocytes and this suggests that activation of replication pathways in these cells may also be associated with viral stimulation. It would have been obvious to one of ordinary skill then to inactivate macrophages as a method of treatment in order to abolish viral replication. Bernstein therefore provides the motivation to combine the references.

Accordingly, the modification of the method of Aldrovandi and Pinto by inactivating macrophages as suggested by Bernstein in order to obtain a method of treating an immunocompromised animal was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 24-30 are rejected under 35 U.S.C. § 103 as being unpatentable over Berenson et al. and Baum et al. taken with Pinto et al. Berenson discloses administration of CD34+ marrow cells to humans having received lethal irradiation. Berenson further discloses that the CD34+ population is capable of reconstituting hematopoiesis in humans. Baum discloses that the CD34+ cell population is the hematopoietic stem cell population. Berenson and Baum differ from the claims in that the reference fails to disclose decreasing endogenous macrophages. However, the secondary reference, Pinto, cures the deficiency. Pinto discloses

use of DMDP to inactivate the endogenous macrophages. Use of PBLs is obvious over the use of bone marrow cells since both sources would contain the CD34+ stem cells. Further, it is well known that bone marrow transplantation results in release of hematopoietic cells into the peripheral circulation of the human. CD34+ cells are stem cells and by definition are capable of reconstituting hematopoiesis in humans thereby giving rise to CD4+ T cells. Pinto provides the motivation to combine the references since Pinto discloses the DMDP inactivates the macrophages, can inhibit the humoral immune response and stimulates leukocytosis. One of ordinary skill would be interested in treating and HIV patient with DMDP since DMDP stimulates lymphocyte proliferation and HIV-1 patients are deficient in CD4+ T cells.

Accordingly, the modification of the method the method of Baum and Berenson by using DMDP as suggested by Pinto in order to obtain a method of restoring hematopoietic cells to an immunocompromised human was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 31 is rejected under 35 U.S.C. § 103 as being unpatentable over Baum et al. taken with Pinto et al. Baum discloses transplantation of human bone marrow into SCID mice and identification of a human hematopoietic stem cell population. Baum differs from the claim in that the reference fails to disclose decreasing endogenous macrophages. However, the secondary reference, Pinto, cures the deficiency. Pinto discloses that DMDP inactivates macrophages. It would have been obvious to

one of ordinary skill to modify the method of Baum by using DMDP in view of the teachings of Pinto that DMDP causes leukocytosis of lymphocytes and PMN and otherwise augments the immune responses by diminishing the humoral immune response, thereby prolonging the life of the engrafted tissue.

Accordingly, the modification of the method of Baum by using DMDP as suggested by Pinto in order to obtain a method of improving engraftment efficiency was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800